

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
ALDICARB (TEMIK)

Chemical Code # 000575, Tolerance # 00269
SB 950 # 130

February 10, 1987

Revised 12/9/87, 10/11/88, 3/1/90, 8/13/91, 1/29/92, 4/28/92, 9/19/94, 1/9/97, and 11/20/98

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effect (not oncogenicity)
Chronic, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosomal effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time, however some neurotoxicity studies have been submitted and reviewed; some found acceptable

Toxicology one-liners are attached.

All relevant record numbers through 160095 (Document No. 269-253) were examined. This examination includes all relevant records on file as of 11/20/98.

In the record numbers in one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

This toxicology summary update is by Aldous, 11/20/98. (filename t981120.wpd)

Toxicology data submitted for metabolites, particularly aldicarb sulfoxide and aldicarb sulfone, are included in this Summary. These pages contain summaries only. Individual worksheets should be reviewed as they may contain additional effects.

II. TOXICOLOGY SUMMARY

COMBINED, RAT

****269-222 127607** "Combined Chronic Toxicity and Oncogenicity Study in Rats with Aldicarb Technical", (J. A. Trutter, Hazleton Washington, Inc., HWA 656-151, 11/24/93). Aldicarb technical, purity 99.7%; 0, 1, 10 or 30 ppm in diet. CrI:CD*BR rats, 70/sex/group, were treated for 2 years. An additional 10/sex/group were designated for a 1-yr interim sacrifice. NOEL = 1 ppm (RBC and plasma cholinesterase inhibition in males, minor increase in alopecia in females). A NOAEL of 10 ppm for systemic effects (exclusive of cholinesterase inhibition) is supportable. Characteristic findings at 30 ppm in both sexes included substantial body weight decrements, lesions of the iris (damage to sphincter muscles, to stroma of the iris, and to capillary system), and "limited use of the tail" (tail is limp, with "apparent hyposensitivity and analgesia": sometimes accompanied by swelling, sores, or loss of tip of tail). In addition, particularly females had increased incidence of alopecia. Study indicates a "possible adverse effect" due to the unusual ophthalmology (lesions of the iris) and the puzzling "limp tail" syndrome. Study is **acceptable**. No oncogenicity was evident. Kishiyama and Aldous, 9/13/94.

NOTE: The primary rat reproduction study (Document No. 269-196, Record No. 112024) found two subcutaneous osteosarcomas in males (1 at 10 ppm and 1 at 20 ppm), as well as a mammary carcinoma in one 10 ppm female. Investigators as well as Medical Toxicology Branch considered the findings to be incidental, however Medical Toxicology Branch awaited the ongoing rat combined study to further address this issue (Aldous, 8/12/91, and Gee, 1/29/92). Note: No oncogenicity was indicated in the combined study (see Record No. 127607). Aldous, 9/19/94.

269-182 097462 and 097463 Information about subchronic studies to select dose levels for Record No. 127607. (See above.)

269-192 093423 One page letter, dated 10/29/91, reporting the finding of "limp tail" in a combined rat study: Record No. 127607, above. Letter was submitted pursuant to 6(a)(2) of FIFRA. Gee, 1/27/92.

CHRONIC RAT (Note: Data gap is filled under COMBINED, RAT, above).

007, 069 034244, "Aldicarb (A), Aldicarb Sulfoxide (ASO), Aldicarb Sulfone (ASO₂) and a 1:1 Mixture of ASO:ASO₂ Two Year Feeding in the Diet of Rats." (Mellon Inst., 1973, Report 35-82), Aldicarb (98.5%), tested at 0.3 mg/kg/day; Aldicarb sulfoxide (99% from #60306), tested at 0.3 or 0.6 mg/kg/day; aldicarb sulfone (>98% from #60306), tested at 0.6 or 2.4 mg/kg/day; aldicarb sulfoxide/sulfone, 1:1, tested at 0.6 or 1.2 mg/kg/day; 36/sex/group for controls and test groups with 16/sex/group of these for interim sacrifice of 4/sex/group at 6 months and remaining survivors at 12 months; fed in the diet. UNACCEPTABLE (organ weights for liver and kidney only, inadequate hematology and clinical chemistry). No adverse effects identified by sponsor. NOEL's \geq high doses for each compound. No adverse effect indicated, not upgradeable as a combined study. (J. Christopher, 5/10/85 and J. Gee, 11/18/87).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Core Minimum". CDFA acceptability status was discussed in the CDFA response to EPA on 12/19/89.

007 922586, Exact duplicate of 034244.

101 050798, Supplement to 034244. Copies of lab notebook pages for diet preparations with

weighing records for active ingredient and feed, individual body weights and food consumption by cage, individual hematocrits and pathology plus a 7-day feeding study to justify the dose selection. (J. Gee, 1/30/87)

127 060306, 062362, 062363, 062364, Supplements to 034244. Includes method of mixing diets at Bushy Run Research Center (Mellon Institute) (#060306), purity and stability of the active ingredients from 8/20/70 to 2/14/72 (#062362), an explanation of the notations on the pages from the notebooks on diet preparation, food consumption and calculation of amount of premix required (#062363) and an explanation concerning the caging of the animals as two per side in a double-sided cage (#062364). (J. Gee, 11/18/87)

128 061987, "Temik^R Aldicarb Pesticide Validation of Procedures for Preparation of Rodent Diets for Toxicology Studies", (Rhone-Poulenc, 8/14/87), supplemental to 034244. Contains data for homogeneity of mixing in Purina Rodent Chow 5002, stability in the diet at room temperature and in the refrigerator at 0, 7 and 14 days, recovery by extraction from the diets and the methods used for assaying aldicarb, aldicarb sulfoxide and aldicarb sulfone. A retrospective study. (J. Gee, 11/18/87)

017, 069 034249, [reviewed as 922587 in Doc.# 017], "Two-year Feeding of Compound 21149 in the Diet of Rats", (Mellon Inst., 10/5/65, Report No. 28-123), Aldicarb, 99.9% was fed in the diet to 36/sex/group at 0, 5, 25, 50 or 100 mg/kg/day. Dietary concentration was adjusted periodically to maintain dose levels. Sixteen/sex/group of these were included for interim sacrifice, 4/sex/group at 6 months and the remaining interim group survivors at 12 months. No adverse effect indicated. UNACCEPTABLE (inadequate dose levels with no depression of weight gain or clinical signs reported; no analysis of diet for stability or homogeneity, poor survival stated to be due to respiratory infections). (J. Christopher, 5/10/85)

Note: Although the diet analysis has been addressed in documents submitted as supplements to 922586, other problems with this study prevent it from being upgradeable. (J. Gee, 11/18/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Core Supplementary". CDFA acceptability status was discussed in the CDFA response to EPA on 12/19/89.

017 038495, 038497, Summary of 034249, 922587.

077 042541, Summary of 034244 and 034249, 922587.

102 050799, Supplement to 034249. Copies of notebook pages of individual body weights, food consumption/4 animals by cage, diet preparation records for weighings. (J. Gee, 2/2/87)

103 052848, Supplement to 034249. Individual gross and microscopic findings plus duplicate of Tables 28-88 and 28-90.

CHRONIC DOG

**137 067491, "One-Year Chronic Oral Toxicity Study in Beagle Dogs With Aldicarb Technical", (Hazleton Laboratories America, Inc., Study # 400-706, 5/31/88), Aldicarb technical (Ref.# 62 JKC 24/HTS 4839AA, sponsor-stated purity = 95.5 %) was fed in the diet to 5 dogs/sex/group at 0, 1, 2, 5 or 10 ppm for 52 weeks. The only treatment related effect was an inhibition of plasma cholinesterase and to a lesser degree RBC cholinesterase in both sexes of groups receiving 2-10 ppm Aldicarb. Nominal NOEL = 1 ppm (based on ChE inhibition). Target organ NOEL > 10 ppm.

The 10 ppm dose level was only marginally high enough to ascertain potential adverse effects of long term exposure to Aldicarb. However, given the extreme acute toxicity (cholinesterase inhibition) of Aldicarb, CDFA does not require a repeat study with higher doses as such a study would probably not substantially add to the toxicological profile of this chemical. No adverse effect. ACCEPTABLE. (H. Margolis and J. Gee, 10/11/88)

192 093424 "One-Year Chronic Oral Toxicity Study in Dogs with Aldicarb Technical." (N. Nicki Hamada, Hazleton Washington, No. 400-706, 10/21/91 for addendum to final report.) The incidences of soft stools and mucoid stools were re-evaluated and the conclusion reached that there was no treatment-related effect, in contrast to the initial report by Hamada. The NOAEL remains 1 ppm (cholinesterase inhibition) as in the initial review. No clinical signs of cholinesterase inhibition. No change in status. Supplementary report. (Gee, 1/27/92)

097 050781, Protocol for Rec.# 067491 (project No. 400-706). (J. Gee, 2/10/87).

269-178 096436 Hamada, N. N., "Subchronic toxicity study in dogs with aldicarb technical". Hazleton Washington, Inc., March 6, 1991. Supplemental study to confirm NOEL's for cholinesterase enzyme inhibition in dogs. Relevant to study 137:067491, above. Investigators applied 20% inhibition as the criterion for demonstration of a treatment effect, and did RBC and plasma cholinesterase assays pretest and at weeks 2 and 5. A NOEL of 0.7 ppm (LEL of 2 ppm) was determined for males and females for plasma cholinesterase. RBC cholinesterase was apparently not affected. Brain cholinesterase inhibition was not measured. This information does not change status of the cited chronic study (acceptable, no adverse effects, apparent cholinesterase NOEL of about 1 ppm, with plasma cholinesterase being most sensitive indicator). No Medical Toxicology Branch worksheet is produced or needed, as this is not a required study and does not change chronic study status. Aldous, 7/23/91.

119 056624, "Two-Week Dose Range-Finding Oral Toxicity Study in Beagle Dogs with Aldicarb Technical", (Hazleton, Vienna, VA, HLA study 400-717, 12-9-86). This was the second range finding study performed to establish a NOEL. Aldicarb technical, 95.5%, was fed in the diet to beagle dogs, 6-8 months of age, 1/sex/group at 0, 0.1, 0.3, 1, 3 or 10 ppm adjusted to 100% active ingredient for 2 weeks. There were no compound related effects observed in mortality, clinical signs, body weight, food consumption, ophthalmology, urinalysis or clinical chemistry except for cholinesterase inhibition. A baseline was established for each animal with three pretest samples. RBC ChE inhibition was 40 to 60 % at 10 ppm at 1 and 2 weeks of treatment, plasma ChE inhibition was 54 to 74% at 10 ppm. Terminal sacrifice showed no brain ChE inhibition. The inhibition was greatest at the end of the 2 hour feeding period until approximately 4 hours after dosing with the percent inhibition decreasing by 6 hours after end of feeding. The study considers this to be a great enough effect to justify 10 ppm as the high dose in a one-year study. Supplemental information. (D. Shimer, 11/10/87 and J. Gee, 11/12/87)

069 034248, "Two-year Feeding of Compound 21149 in the Diet of Dogs", (Mellon Inst., 1/25/66, Report 29-5), Aldicarb, 99.9%; fed in the diet to 3/sex/group at 0, 0.83, 1.67 or 3.33 ppm. No adverse effect reported. NOEL \geq 3.33 ppm. UNACCEPTABLE (no MTD used, no analysis of diet, animals 8 - 20 months at start). No cholinesterase inhibition, but blood samples were taken 12 - 18 hours after removal of food containing aldicarb. J. Christopher, 9/18/85)

Note: Document 269-096 contains cholinesterase values from 2 short-term studies conducted in 1985-86. At 0.06 mg/kg, plasma cholinesterase in males was inhibited by 35% and in females, by 28%; RBC cholinesterase showed less inhibition. At the next higher dose, 0.16 mg/kg, male plasma cholinesterase was inhibited by 49% with much less effect in females. This was presented as justification of the dose selection of 3.33 ppm (approximately 0.1 mg/kg). Gee,

2/10/87.

077 042543, Summary of 034248.

017 922576, Summary of 34248. (J. Christopher, 5/10/85)

097 050785, Supplement to 034248. Stability of aldicarb in dog diet at room temperature and in the freezer. At room temperature, 25-30% was lost in 7 days. (J. Gee, 1/28/87)

104 052849, Supplement to 034248. Individual gross and microscopic findings. (J. Gee, 1/29/87)

103 050800, Supplement to 034248. Copies of handwritten lab notebook pages of cholinesterase measurements, hematocrits, body weight changes, diet consumption, liver and kidney weights at termination, records of weights for diet preparation. (J. Gee, 2/2/87)

ONCOGENICITY RAT (data gap is filled: see COMBINED, RAT)

056 922589, "Bioassay of Aldicarb for Possible Carcinogenicity", (Gulf South Research, 11/1979, for NCI, Report NIH 79-1391), Aldicarb, 99%, fed in the diet at 0, 2 or 6 ppm [approximately 0.3 mg/kg] to 50/sex/treatment group and 25/sex for concurrent controls; analyses showed 1.8 and 5.8 actual content. UNACCEPTABLE (no individual data, no justification of dose selection, no hematology so ineligible for consideration as a chronic or combined study). Possibly upgradeable with submission of missing data. Evaluated as having insufficient information for acceptability and no adverse effect was clearly identified. The incidence of tumors found was not statistically significant compared with concurrent controls. Nominal oncogenicity NOEL \geq 6 ppm. No adverse effect indicated. (J. Christopher, 5/9/85)

NOTE: EPA one-liner not available

077 042545, Summary of 922589.

ONCOGENICITY MOUSE

056 922589, "Bioassay of Aldicarb for Possible Carcinogenicity", (Gulf South Research, 11/1979, for NCI, Report NIH 79-1391), Aldicarb, 99% was fed in the diet at 0, 2 or 6 ppm to 50/sex/treatment group and 25/sex for concurrent control, B6C3F1 mice. UNACCEPTABLE (no individual data, dose selection too low despite a subchronic study). No evidence of carcinogenicity was reported. Nominal NOEL \geq 6 ppm. No adverse effect indicated. (J. Christopher, 5/9/85)

073 034262, "Results of Long-Term Tests for Mouse Skin Carcinogenicity of Three Process Residues, One Epoxide and Three Compounds", (Mellon Inst., Report # 29-34, 4/14/66), Dermal carcinogenesis study in mice; aldicarb, 50% in acetone by skin painting three times weekly for 15 months, reduced to 25% for months 16 - 26 months; no skin tumors reported due to test article. No adverse effect indicated. UNACCEPTABLE (no analysis of dosing solution, dose selection questionable and survival poor). (J. Christopher, 9/23/85)

077 042544, Summary of 034262.

069 034247, "Aldicarb: 18-month Feeding in Diet of Mice, Study I", (Mellon Inst., Report 35-70, 10/4/72), Aldicarb, 98.5%; fed in the diet to CD-1 mice, 44/sex/group, at 0, 0.1, 0.2, 0.4 or 0.7 mg/kg/day, for 77 weeks. Dose range was justified by a preliminary 1-week dietary study, in which 4/10 mice died at 1.2 mg/kg/day. No adverse effect reported. NOEL > 0.7 mg/kg/day. The increased incidence in liver tumors in male mice compared with controls was not confirmed in a repeat study in males in which two groups of concurrent controls were used (see 034246 below.) Initially reviewed as UNACCEPTABLE (based on the lack of diet analysis for content, stability and homogeneity) but possibly upgradeable. (J. Christopher, 9/18/85 and J. Gee, 11/19/87)

077 042546, Summary of 034247.

069 034246, "Aldicarb: 18-month Feeding in the Diet of Mice, Study II", (Carnegie-Mellon Inst., Report 37-98, 11/14/74), Aldicarb, 99.2%; fed in the diet for 18 months at 0, 0.1, 0.3 or 0.7 mg/kg/day, 50 per group with two concurrent controls of 50 each, males only in study II to investigate the incidence of liver tumors seen in males in Study I in which both sexes were exposed; no toxicity and no adverse effect reported. This study used males only but was designed as a supplement to 034247. Nominal NOEL \geq 0.7 mg/kg/day. (J. Christopher, 9/19/85 and J. Gee, 11/18/87.)

069 034245, Addendum to 34246, 34247. Reanalysis of tumor incidence data. Report 39-55.

106, 107 050804, 050805, Addenda to 034246 and 034247. Copies of lab notebooks containing individual body weights by dose and cage, food consumption per cage for intervals of approximately 2 weeks, individual pathology, diet room records for weights of AI and feed to achieve a calculated percentage to maintain the target dose. (J. Gee, 2/3/87)

127 060306, 062362, 062363, Supplemental to studies conducted at Mellon Institute addressing stability of the test material and an explanation of the notebook notations. (J. Gee, 11/18/87)

128 061987, Supplemental report to studies conducted at Mellon Institute on the stability of aldicarb at room temperature and in the refrigerator on days 0, 7 and 14, homogeneity of mixing and recovery from the diet for quantitation. (J. Gee, 11/18/87)

SUMMARY: No evidence of an oncogenic effect for aldicarb has been reported in mice. The increase in liver tumors in male mice suggested in the study by Mellon Institute, No. 35-70, could not be confirmed in a second study in which a larger number of concurrent controls was used. In addition, the NCI study conducted at Gulf South Research Institute in 1979 did not report any effect in a different strain of mice. Initially, the problem of dietary stability and actual content over the exposure period prevented the studies from being acceptable. With the submission of documents 127 and 128, the questions about the diet have largely been resolved and are adequate to fulfill the data requirement. Although no one study is acceptable, the collective data from the several studies provide sufficient evidence on the lack of an oncogenic effect. (J. Gee, 11/18/87).

REPRODUCTION RAT

** 269-196 112024 "Two-Generation Reproduction Study in Rats with Aldicarb." (J. K. Lemen, Hazleton Washington, HWA Study No. 656-157, 12/17/91). Aldicarb technical, lot No.

25-DEQ-89, 99.7%, was fed in the diet at 0 (diet), 2, 5, 10 or 20 ppm, to 26/sex/group CrI:CD BR rats. Rats were mated for two litters per generation, two generations. There were no effects on reproductive parameters other than pup viability during days 0 - 4 at 20 ppm. Pup weight was also lower at this dose. Mean body weights of breeders were lower at 20 ppm, especially in males. Plasma and erythrocyte cholinesterase levels were determined pretreatment and at termination of adults. Inhibition was found at 10 and 20 ppm. No brain cholinesterase was measured. One male from the 10 and 20 ppm groups of the F0 generation had "poorly differentiated mesenchymal tumors" in subcutaneous tissue diagnosed as osteogenic sarcomas. One female in the F0 10 ppm group had a mammary gland carcinoma. No tumors were found in the F1 adults, suggesting that the above tumor findings were likely to be incidental. No adverse effect. Reproduction NOEL = 10 ppm (body weight, pup weight and viability); cholinesterase NOEL = 5 ppm. No adverse reproductive effects. ACCEPTABLE. Gee, 1/29/92.

NOTE: Rhone Poulenc Ag Co. sent CDFA a letter on 1/14/91 advising the department of the unusual occurrences of the above osteogenic sarcomas in compliance with FIFRA section 6(a)(2) requirements. Careful examination of tumor data in the subsequent combined study (Record No. 127607) did not indicate an oncogenic response. Aldous, 9/14/94.

269-183 097387, 097388 General protocols for pilot and 2-generation reproduction studies (see especially Record No. 112024).

269-180 097007 Tyl, R.W., Marr, M.C., and Myers, C.B., "Preliminary evaluation of aldicarb excretion in the milk of lactating CD* rats exposed to aldicarb in the diet". Research Triangle Institute, Research Triangle Park, NC, 3/22/91. (Ancillary study undertaken following results of the above pilot reproduction study, with protocol in Vol. 183, Record 097387). Pregnant CD rats were dosed with 0 or 20 ppm aldicarb in diet (25 and 37 sperm-positive females, respectively) from gestational day 7 until day 4 post partum. At that time, milk samples were collected from dams, and assayed for aldicarb, and for the two major metabolites: the sulfoxide and the sulfone. Ten pooled samples of milk from treated dams were analyzed. Only 1 had detectable aldicarb, and 5 had measurable sulfoxide, and 6 had measurable sulfone. Based on an approximation of 1.5 ml/pup at day 4, estimated intake on day 4 was 0.037 mg aldicarb, 0.025 mg aldicarb sulfoxide, and 0.031 mg aldicarb sulfone, per pup. Investigators concluded that intake of these chemicals in milk may have made significant impact on health of pups, and may have accounted for part of the high mortality experienced in the range finding reproduction study (37% between days 0 and 4 in that study). No Medical Toxicology Branch worksheet is needed at this time. See Record No. 112024, above, and associated worksheets. Gee, 1/29/92.

014, 017, 074 922591, [changed from 922590], "Results of a Three Generation Reproduction Study on Rats fed Compound UC-21149 in Their Diet." (Mellon Inst., 12/7/64, Report No. 27-158), Aldicarb, 99.9%, fed in the diet at 0, 0.05 or 0.10 mg/kg, to 16 - 20 females per group for three matings - 8 or 10 males per group; mated 1 male: 2 females, males rotated 3 times per week. UNACCEPTABLE (only two doses and no toxicity apparent, no histopathology on breeders, no analysis of diet for content or stability). Nominal reproductive NOEL \geq 0.1 mg/kg. No adverse effect indicated. (J. Christopher, 5/10/85)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Core Supplementary". CDFA acceptability status was discussed in the CDFA response to EPA on 12/19/89.

017 038496, Summary of 922591.

103 052847, Supplement to 922591. Pathology summary on F3a males and females of control and high dose groups.

077 042550, Summary of 922591.

104 050801, Supplement to 922591. Copies of lab notebook pages with data for individual dams with number, sex and individual weanling weight of pups, dam weights, male body weights and F1 rotation schedule. (J. Gee, 2/2/87)

074 034264, "Aldicarb Inclusion in the Diet of Rats for Three Generations and a Dominant Lethal Mutagenesis Test", (Carnegie-Mellon Inst., 10/28/74, Report no. 37-90), Aldicarb, 99.2%; fed in the diet to 10 males/20 females per group at 0, 0.2, 0.3 or 0.7 mg/kg/day, three matings. UNACCEPTABLE, not upgradeable (no necropsy on F0 or F1 parents, inadequate number for histopathology from F2a parents). Reproduction NOEL \geq 0.7 mg/kg/day (HDT). No adverse effect indicated at doses tested. See 034265 for dominant lethal section below. (J. Christopher, 9/25/85 and J. Gee, 11/18/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Core Minimum". CDFA acceptability status was discussed in the CDFA response to EPA on 12/19/89.

105 050802, Supplement to 034264. Copy of lab notebook pages of weighings for diet preparation, summary of pathology findings and individual pathology including reproductive organs for F2a parents, 5/sex for control and high dose groups and pathology for F3a weanlings, 5/sex for control and high dose groups. (J. Gee, 2/2/87)

127 060306, 062362, 062363, Supplements to 034264. Includes method of mixing diets at Bushy Run Research Center (Mellon Institute) (#060306), purity and stability of the active ingredients from 8/20/70 to 2/14/72 (#062362), an explanation of the notations on the pages from the notebooks on diet preparation, food consumption and calculation of amount of premix required (# 062363). (J. Gee, 11/18/87)

128 061987, "Temik^R Aldicarb Pesticide Validation of Procedures for Preparation of Rodent Diets for Toxicology Studies", (Rhone-Poulenc, 8/14/87). Supplemental to 034264. Contains data for homogeneity of mixing in Purina Rodent Chow 5002, stability in the diet at room temperature and in the refrigerator at 0, 7 and 14 days, recovery by extraction from the diets and the methods used for assaying aldicarb. (J. Gee, 11/18/87)

TERATOGENICITY, RAT

153 072063, "Developmental Toxicity Evaluation of Aldicarb Administered by Gavage to CD* (Sprague-Dawley) Rats", (Bushy Run Research Center, Export, PA., Report # 51-551, 11/14/88). Technical grade aldicarb (purity = 99.5%) was administered daily by gavage on gestation days 6 through 15 at 0 (deionized water), 0.125, 0.25, and 0.5 mg/kg/day to mated CD* female rats (25/group). **No adverse effect. Maternal NOEL = 0.125 (Significant clinical signs and increased mortality were observed at 0.5 mg/kg. Reduced bodyweight, bodyweight gain and increased liver weight were observed at 0.5 mg/kg. Food consumption and corrected maternal bodyweight change were significantly decreased at \geq 0.25 mg/kg.) **Developmental NOEL = 0.250 mg/kg/day** (Decreased mean fetal weight along with an increased incidence of visceral malformations (dilated lateral ventricle with tissue depression) and an increased incidence of skeletal variations

(reduced ossification of the 6th sternebra) was observed at 0.5 mg/kg.) **Acceptable.** (Green & Silva, 2/22/90; Silva, 4/13/92).

072 034257, "Insecticide Temik: Teratogenic Potential in Rats", (Mellon Inst., 9/6/66, Report 29-81), Aldicarb, 100.5%; 10-11/group fed 0, 0.04, 0.2 or 1.0 mg/kg/day in the diet on one of three regimens - mating through sacrifice on day 20/21 of gestation or day 21 of lactation, mating (day 0) to day 7 of gestation or days 5 - 15 of gestation; half the dams in each group were killed on day 20/21 of gestation and fetuses examined for skeletal defects (no data presented), the other half allowed to litter and raise offspring to weaning. No effect reported but 1 mg/kg/day stated as oral LD50. Maternal and Developmental NOEL \geq 1 mg/kg/day. UNACCEPTABLE (no visceral examination of fetuses). This study is not upgradeable, no additional data are requested and the study must be replaced by a study conducted under current guidelines. (J. Christopher, 9/23/85, and J. Parker, 4/29/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes that EPA had required a replacement study. No such study has yet been received by DPR as of 8/12/91 (see 153:072063, above).

077 042549, Summary of 034257.

TERATOGENICITY, RABBIT

**057 001057, "Teratology Study in Rabbits", (IRDC, Report # 369-107, 10/11/83), Aldicarb, 99%; given by oral gavage at 0, 0.1, 0.25 or 0.5 mg/kg/day, days 7 to 27, to 16 artificially inseminated rabbits per group. Rabbits were received in three shipments; animals were exposed in two phases due to a misdosing at day 7, which necessitated replacement of 8 does/group. ACCEPTABLE. Maternal NOEL = 0.1 mg/kg/day [weight loss, also equivocal effect of hydroceles on oviducts (with incidence of 0, 0, 2, and 2 in increasing dosage groups)]; developmental NOEL \geq 0.5 mg/kg/day. No adverse effect. (J. Christopher, 5/10/85 and J. Gee, 1/28/87); re-examination with minor clarification in 1-liner by Aldous, 4/13/92, with no new worksheet).

EPA 1-liner (ref Record No. 001057): Guideline. Teratogenic NOEL > 0.5 mg/kg/day (HDT), maternal NOEL = 0.25 mg/kg/day (decreased body weight, pale kidneys and hydroceles on the oviducts), fetotoxic NOEL < 0.1 mg/kg/day (viable fetuses/doe and number of implantations/doe were decreased.)

Note: Investigators noted that all treatment groups had fewer implantations per dam than did controls. This was not dose-related, the highest decrement (and the only one which was statistically significant compared to concurrent controls) was at the low dose level. The control group had well above the mean historical range of implantations. The original CDFA reviewers considered this finding to be incidental. Subsequent re-examination by C. Aldous confirms that CDFA/DPR conclusion (no new worksheet) 4/13/92.

097 050780, Supplement to 001057. Protocol for preparation of dosing solutions from IRDC, study schedule with dates and copies of daily records describing how dosing solutions were prepared and diluted for each dose. Submission upgrades 001057 to ACCEPTABLE. (J. Gee, 1/28/87)

097 050786-050788, Supplement to 001057. Stability data in aqueous buffers. Applies also to # 034251, 034252 and 034253 (genotoxicity studies).

072 034259, Dose range-finding study for 001057.

GENE MUTATION

Microbial systems

070 034254, "Ames Salmonella/Microsome Plate Test", (Pharmakon, 6/20/80, Ph 301-UC-004-80), Aldicarb, no purity stated; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation, in duplicate or triplicate at 0, 50, 166, 500, 1666 or 5000 ug/plate. No adverse effect indicated (No increase in reversion rate). UNACCEPTABLE. (J. Gee, 9/18/85)

EPA 1-liner: Downgraded to unacceptable. Aldicarb dissolved in DMSO at 50 to 5000 ug/plate. Negative in Salmonella....

077 042547, Summary of 034254.

Mammalian systems

**070 034251, "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay", (Pharmakon, 3/85, Ph-314-UC-003-84), Aldicarb, Lot # 4839AA, tested with CHO with and without activation at 0, 1000, 2000, 3000, 4000 or 5000 ug/ml, 5 hours; duplicates per concentration. No adverse effect (no increase in mutation frequency reported). ACCEPTABLE. (J. Gee, 9/19/85)

CHROMOSOMAL ABERRATIONS

**269-175 095268, "Mutagenicity Test on Aldicarb Technical in the Mouse Bone Marrow Cytogenetic Assay", (J. L. Ivett, Hazleton Laboratories America, HLA Study No. 12010-0-451, 9/28/90). Aldicarb Technical, purity 99.7%, at doses 0 (deionized water), 0.1, 0.2, or 0.4 mg/kg was given in a single oral dose to 5 ICR mice/sex/dose group. Additional animals from a secondary high dose treatment group replaced those high dose animals that died in the primary group. Bone marrow was harvested at 6, 18, and 30 hours after dosing. Clinical signs of dyspnea and tremors were seen in the high dose group after dosing with a return to normal in survivors. There was no increase in the incidence of chromosomal aberrations or a clear effect on the mitotic indices. NEGATIVE AND ACCEPTABLE. (Kishiyama and Gee, 7/30/91)

269-175 095267. Dose range-finding study for 175 095268. No worksheet. (Gee, 8/12/91)

269-233 135454 Tyl, R.W., M.C. Marr, and C.B. Myers, "Modified dominant lethal evaluation of Aldicarb administered in the feed to CD® (Sprague-Dawley) rats," Research Triangle Institute, Research Triangle Park, NC, 2/21/95. CrI:CD®[SD]BR male rats, 40/group, were dosed with 0, 7.5, 15, or 30 ppm aldicarb technical (98.9% purity) in diet for 10 weeks. Untreated females were mated 1:1 with the treated males for 1-week periods. The first series of 40 females per group was mated to respective males immediately after the dosing period. The second series was mated to the males the following week. Females were sacrificed on day 15 of gestation for uterine and ovarian inspections for dominant lethal effects. In addition to the groups indicated above, ten control males and ten 30 ppm males were dosed for four days, then sacrificed for assessment of RBC, plasma, and brain cholinesterase. Respective cholinesterase activities were 64%, 11%, and 69% of controls. Fine tremors of up to five high dose rats were noted during daily clinical observations, indicative of direct cholinesterase effects. Reduced food consumption and reduced body weights were dose-related at 15 to 30 ppm. There were no dominant lethal effects. Study is not acceptable, due to lack of positive control data. Contemporary positive

control data from the same laboratory may be submitted as part of a request for an upgrade. Aldous, 10/25/96.

074 034265, "Aldicarb, Inclusion in the Diet of Rats for Three Generations and a Dominant Lethal Mutagenesis Test", (Carnegie-Mellon, 10/28/74, Report 37-90). Dominant lethal as part of a 3-generation reproduction study; exposed continuously in utero at 0, 0.2, 0.3 or 0.7 mg/kg/day; no positive control. No adverse effect reported. UNACCEPTABLE (protocol). (J. Christopher, 9/24/85)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes that EPA does not accept this study, although EPA considers the data gap filled by another study on aldicarb sulfone (possibly this is study 131:065863).

105 050803, Supplement to 034265. Copy of lab notebook pages for mating schedule with animal numbers for the dominant lethal section of the reproduction study. (J. Gee, 1/29/87)

077 042548, Summary of 034265.

070 034252, "Mutagenicity Evaluation of Aldicarb Technical 93.47% in the Mouse Bone Marrow Cytogenetic Assay: Final Report", (Litton Bionetics, 3/83, LBI No. 22202, #7198.) Aldicarb, 93.47%; injected i.p. in a single injection at 0, 0.001 or 0.01 mg/kg or 5 doses at 0.01 mg/kg; sacrifice of 5/sex/group at 6, 24 or 48 hours; scored approximately 50 cells per animal. No adverse effect reported. UNACCEPTABLE (no evidence of MTD). (J. Gee, 9/18/85)

EPA 1-liner: unacceptable, nonclastogenic in mouse bone marrow cytogenetic assay.

097 050784, Supplement to 034252. Individual animal and cell data.

097 050783, "Effect of Aldicarb (Temik) a Carbamate Insecticide, on Chromosomes of the Laboratory Rat", (University of Cairo, published in Egypt. J. Genet. Cytol. 11: 143-151 (1982). Aldicarb, 98.9%; male rats, 6/group, were injected once i.p. at 0.00121, 0.00666 or 0.0121 mg/kg (considered 1/10 MTD or usage level and MTD with an intermediate dose) or 5 daily injections at each dose; sacrificed at 6, 24 or 48 hours after acute injection and 6 hours after multiple dosings. **Possible adverse effect indicated** (increase in aberration at several times, all doses). UNACCEPTABLE (no individual data, one sex only without justification, tables are confusing for control values).

Note: Publication was submitted as justification for the doses selected in 034252. J. Gee, 1/28/87.

127 062365, Supplement to 050783. A Letter from Dr. R. Naismith discussing the problems with Record # 050783 and he questions the conclusions of the authors. A major problem he identified was the pooling of control data from animals sacrificed at different times.

SUMMARY: The data in the publication (# 050783) in Table 2 are unclear, especially in terms of the statistics and values indicated as significant compared with other values which are similar but not significant. There appears to be a positive response for aberrations and numerical changes at several time points and for several types of aberrations. The study in the mouse conducted by Litton (# 034252) at similar but slightly lower doses (0.01 compared with 0.0121) did not confirm these results. The CDFA reviewer had no means of determining if one or the other study contained an artifact or technical problem causing the different results or whether there was a species difference. The source of the aldicarb was Union Carbide in both studies. (J. Gee, 11/19/87). With the submission of # 095268 with negative results in the mouse, the weight of

evidence indicates that aldicarb given at doses causing clinical signs does not induce chromosomal aberrations. (Gee, 8/13/91).

DNA DAMAGE

**070 034253, "Rat Hepatocyte Primary Culture/DNA Repair Test", (Pharmakon Res. Int., 1/24/84, Ph 311-UC-005-83), Aldicarb technical, added to medium at 0, 0.33, 1.0, 3.33, 10.0, 33.3, 100.0, 333.3, 1000, 3333.3 or 10,000 ug/well with 2 ml per well; 333.3 the highest concentration scored; triplicate cultures, 20 cells/slide scored for grains. ACCEPTABLE. No adverse effect (no increase in unscheduled DNA synthesis was reported). (J. Gee, 9/18/85)
EPA 1-liner: Acceptable, inactive in the primary rat hepatocyte UDS assay.

NEUROTOXICITY (HEN STUDIES)

Not required at this time, however some data have been submitted (below). Note the extensive section on rodent neurotoxicity studies below.

071 034255, Johnson, H.E., "Temik (Technical Grade Compound 21149), Demyelination Potential in Chickens", (Mellon Inst., Report 29-90, 9/22/66), summary of a study in which 6 White Leghorn hens/group received "peroral" (presumably stomach tube) doses of 9 mg/kg/day (the LD50), or 4.5 or 2.25 mg/kg/day for 30 days. Survivors were held for an additional 30 days for continued observations. Histology was performed on brain, spinal cord, and sciatic nerve. Apparently 4/6 of the 9 mg/kg/day hens died within 2 wk, and 4/6 of the 4.5 mg/kg/day hens died within the 30-day treatment period. Effects noted during the initial few days of treatment included salivation, ataxia, and malaise: these effects subsided within a few days. There were no findings in aldicarb animals suggestive of delayed distal neuropathy. TOCP was used as a positive control, with expected delayed effects. **No adverse effect reported. Unacceptable** (insufficient detail presented for an independent review; many variations from modern guidelines). (J. Christopher, 9/26/85; 1-liner rewritten by Aldous, 4/13/92).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes that EPA has accepted the complete report summarized in 071:034255.

NEUROTOXICITY (RAT STUDIES ON ALDICARB AND MAJOR METABOLITES)

Three acute neurotoxicity studies on aldicarb and major metabolites are:

1. Bio-Research Laboratories Ltd. Project ID #97235, "An acute study of the potential effects of orally administered aldicarb, technical grade, on behavior and neuromorphology in rats", DPR Record #133263.
2. Bio-Research Laboratories Ltd. Project ID #97351, "An acute study of the potential effects of orally administered aldicarb sulfone on behavior, neurochemistry, and neuromorphology in rats", DPR Record #135084.
3. Bio-Research Laboratories Ltd. Project ID #97350, "An acute study of the potential effects of orally administered aldicarb sulfoxide on behavior and neuromorphology in rats", DPR Record #135083.

Project ID 97352 (Record No. 133272) was designed to evaluate the course of cholinesterase inhibition due to aldicarb and its major sulfoxide and sulfone metabolites. Due to the comparatively slow recovery of cholinesterase activity in aldicarb sulfone groups over the 8-hr time frame of that study, a follow-up study for this metabolite was done employing a longer post-treatment evaluation period. That report follows immediately after Project ID 97352 (with continuous pagination, and as part of the same DPR record) as Laboratory Project ID 97351.1.

Additional preliminary studies conducted to establish test conditions for the above acute neurotoxicity studies include two studies of survival and clinical observations in small numbers of rats exposed to aldicarb and the two metabolites (DPR Record Nos. 133270 and 133271: Bio-Research Laboratories Ltd. Project ID #s 97277 and 97358, respectively).

Another study evaluated abbreviated FOB parameters in rats exposed to a range of aldicarb concentrations. That study (Record No. 133267, Bio-Research Laboratories Ltd. Project ID 97236) established dose levels and optimal intervals between dosing and FOB and motor activity evaluations for the primary acute study on aldicarb (Record No. 133263).

NOTE: Four studies which follow were upgraded to acceptable status after receipt of valid positive control data, as summarized in the following 1-liner. The titles of the six studies follow the 1-liners of the various rat neurotoxicity studies on aldicarb and its primary metabolites.

269-248 to -253 160090 to 160095 [All 6 were authored by P. Beyrouthy]. The first 5 of the submissions sent to upgrade the 4 cited studies were dated Nov. 4, 1994. The last submission (Record No. 160095) was dated 11/19/92, and is not essential for the upgrade. Upgraded records are:

Document #	Record #	Test Article	Neurotoxicity Study Type
269-224	133263	Aldicarb	Acute
269-231	134083	Aldicarb Sulfoxide	Acute
269-232	134084	Aldicarb Sulfone	Acute
269-237	142239	Aldicarb	Subchronic (13-wk)

The first 5 newly submitted records had previously been accepted by DPR as valid positive control data. These records were sent in support of another active ingredient of the same sponsor (Rhone-Poulenc Ag Company). The first 5 new submissions allow the 4 cited studies to be upgraded: the original DPR reviews had indicated that valid positive control data would allow upgrades to acceptable status. The individual 1-liners in the Summary of Toxicology Data have been changed to reflect acceptable status. Aldous, 11/20/98.

**269-224 133263 Robinson, K., W. Brooks, and B. Broxup, "An acute study of the potential effects of orally administered aldicarb, technical grade, on behavior and neuromorphology in rats", Bio-Research Laboratories Ltd., Laboratory Project No. 97235, 9/28/94. CrI:CD®(SD)BR rats, 22/sex/group, were administered aldicarb, 99.0% purity, by a single gavage dose in water solution at 0, 0.05, 0.1, or 0.5 mg/kg. Twelve/sex/dose were designated for FOB and motor activity testing at prestudy, day 0 (beginning within 1 hr after dosing), day 7 and day 14. On day 15, 6/sex of these rats were perfused for neuropathology examinations. Of the rats not assigned to FOB and motor activity testing, 5/sex/group were sacrificed at about 0.75 hr after dosing, and the other 5/sex/group at 8 hr after dosing. These rats were used to assess cholinesterase activities at approximately peak inhibition time, and at a time expected to be near complete recovery. Six/sex/group of the FOB/motor activity rats were perfused for neurohistopathology on day 15. Brain and spinal cord and limited other tissues were embedded in paraffin, and most peripheral nervous tissues were embedded in epoxy. There is no firm NOEL for plasma cholinesterase inhibition, based on dose-related inhibition (sizable, but not statistically significant at the low dose). The NOEL for FOB findings is 0.05 mg/kg, based on slight tremors and slight

increase in respiratory rate in one 0.1 mg/kg male (consistent with high incidence of these findings at the high dose). Common findings at 0.5 mg/kg also included ataxia, lying down on ventral surface, reduced locomotor activity, reduced arousal level, reduced rearing behavior, increased lacrimation and salivation, and reductions in tail pinch reflex, in forelimb and hindlimb grip strength, and in body temperature. Histopathology was negative, and no toxicity persisted beyond day 0. Originally not accepted, due to lack of positive control data. **Accepted** on receipt of requested data in Record Nos. 160090 to 160095, above. No adverse effects. Aldous, 1/9/97 and 11/20/98.

269-225 133267 Robinson, K., W. Brooks, and B. Broxup, "A time of peak behavioral effects study of a single oral administration of Aldicarb, Technical Grade, in rats", Bio-Research Laboratories Ltd., 9/27/94, Project No. 97236. This was a pilot study to optimize conditions for an acute neurotoxicity study. Sprague-Dawley rats were evaluated to set dose levels for aldicarb technical, considering behavior effects in an abbreviated FOB, clinical signs, survival, and cholinesterase inhibition. Dose levels ranged from 0.1 to 0.8 mg/kg in the various phases of the study. A dose of 0.8 mg/kg caused deaths in 2/3 males and 2/3 females. Two out of ten males died at 0.6 mg/kg. FOB changes typical of the 0.4 to 0.8 mg/kg level included decreased arousal, ataxia or overall gait incapacity, decreased or absent locomotor activity, tremors of head, body, or limbs, salivation, lacrimation, altered respiratory rate or gasping, and urinary staining. These signs were particularly marked at 0.5 to 1 hr after dosing, then gradually decreased over the next few hours. By 8 hr, 0.4 mg/kg rats had normal FOB patterns, but some 0.8 mg/kg survivors still showed some of the above symptoms. Plasma cholinesterase inhibition was strongest between 0.5 and 2 hr, with substantial recovery over the next few hours. A similar pattern, but lesser degree, occurred for RBC cholinesterase. Brain cholinesterase, measured at 24 hr after exposures up to 0.8 mg/kg, did not show treatment effects. Based on these findings, dose levels selected for the acute rat neurotoxicity studies included dose levels of 0.05, 0.1, and 0.5 mg/kg. FOB measurements would be 0.5 hr after treatment, and motor activity measurements would begin 1 hr postdosing. Aldous, 1/9/97.

269-226 133270 Robinson, K., and B. Broxup, "An acute benchmark-dose toxicity study of orally administered aldicarb, technical grade, in rats", Rhone-Poulenc, 9/27/94. Project ID # 97277. This was a limited scope study, serving to set dose levels for Record No. 133267, which was the full scale rangefinding study for acute neurotoxicity assessment. The present study used two Sprague-Dawley rats/sex at single gavage dose levels of 0.125, 0.25, 0.50, 0.75, 1.0, and 1.5 mg/kg. Survival, clinical observations, and b.w. effects were evaluated. Within 1 hr of dosing, 3/4 high dose rats and 1/4 of the 1.0 mg/kg rats died. All rats at 0.50 mg/kg and above had tremors. Clinical signs like those reported in Record No. 133267 were common at 0.5 mg/kg and above in males and at 0.75 mg/kg and above in females. These dose levels were associated with marked but transient b.w. losses. Aldous, 10/29/96.

269-226 133271 Brooks, W. and B. Broxup, "An acute benchmark-dose toxicity study of orally administered aldicarb sulfone and aldicarb sulfoxide in rats", Rhone-Poulenc, 9/28/94. Project ID # 97358. This was a limited scope study, covering the parameters measured in Record No. 133270, as applied to these two major aldicarb metabolites. The present study used two Sprague-Dawley rats/sex/compound at single gavage dose levels of 1, 5, 10, 20, 30, 40, and 50 mg/kg for aldicarb sulfone, and 0.125, 0.25, 0.50, 0.75, 1.0, and 1.5 mg/kg for aldicarb sulfoxide. One male given 30 mg/kg aldicarb sulfone died, as well as all 40 to 50 mg/kg males. One female given 40 mg/kg aldicarb sulfone died. Aldicarb sulfoxide deaths were limited to the 1.5 mg/kg level, at which dose 3/4 rats died. Remarkable body weight decrements were observed at or above 10-20 mg/kg of the sulfone and 0.5 mg/kg of the sulfoxide. The most sensitive clinical observation parameter was tremors, usually evident in head, body, and limbs, at 5 mg/kg and

above in all rats with the sulfone. In sulfoxide rats, tremors were found in one 0.125 mg/kg male and in all rats at 0.25 mg/kg and above. Other cholinergic signs such as salivation and staining were seen in higher dose levels with both test compounds. Aldous, Jan. 9, 1997.

269-227 133272 Brooks, W. and B. Broxup, "An acute study of the time course of cholinesterase inhibition by aldicarb technical, aldicarb sulfoxide and aldicarb sulfone in the rat", Bio-Research Laboratories Ltd., 9/29/94, Project No. 97352. Eighteen CrI:CD@(SD)BR rats/sex/group were dosed once by gavage with vehicle (water), Aldicarb Technical, purity 98.9% (0.25 or 0.50 mg/kg/day); Aldicarb Sulfone, purity 99.9% (10 or 20 mg/kg/day), or Aldicarb Sulfoxide, purity 98.9% (0.25 or 0.50 mg/kg/day). Six rats/sex/group were killed at 1, 4, or 8 hr after dosing. Primary parameters studied were clinical observations at time of sacrifice and cholinesterase inhibition in blood and brain regions. Tremors were noted in all treated groups at 1 hr after dosing, however only in the 20 mg/kg/day sulfone group did tremors persist as long as 8 hr. Salivation and fur wetness or staining were common in all groups at 1 hr, but not at 4 hr. RBC and especially plasma cholinesterase activities were markedly inhibited at 1 hr in all treated groups. There was variable inhibition of brain cholinesterase in all groups at 1 hr, with cerebellum as the most affected region and caudate/putamen not measurably affected except by the sulfone. There was substantial recovery in aldicarb and sulfoxide groups for RBC, plasma, and all brain region cholinesterase activities by 4 hr. Brain, RBC, and plasma cholinesterase activities were still substantially reduced at 8 hr in sulfone-treated rats. Thus, an additional study with sacrifice times of 24 and 48 hr was conducted with the sulfone (beginning on p. 207 of this record, reviewed separately). This is a valid ancillary study not applicable to SB-950 data requirements. Aldous, 1/9/97.

269-227 133272 (the second of 2 reports under this record number) Brooks, W. and B. Broxup, "An acute study of the potential effects of orally administered aldicarb sulfone on neurochemistry in rats", Bio-Research Laboratories Ltd., Project No. 97351.1, 9/29/94. Ten CrI:CD@(SD)BR rats/sex/group were dosed once by gavage with vehicle (water) or Aldicarb Sulfone, purity 99.9% (0, 10 or 20 mg/kg/day). Five rats/sex/group were killed at 24 hr after dosing, and equal numbers were killed at 48 hr. As in the primary study (the first report under this record number), primary parameters studied were clinical observations at time of sacrifice and cholinesterase inhibition in blood and brain regions. Blood samples were taken at both termination times, and additionally at 1 and 8 hrs for the 24-hr groups. Effects persisting 24 hr or longer were limited to 20 mg/kg/day rats, including: significant body weight decrements (48 hr, both sexes), plasma cholinesterase inhibition (42% and 37% of control levels at 24 hr for males and females, respectively), significant cholinesterase inhibition in most brain regions (24 hr groups only, the most significant effect being 50% inhibition of control cerebellar cholinesterase activity in females), and yellow fur staining in 2/10 females. At 48 hr, plasma cholinesterase activity was no longer statistically significantly reduced in either sex, however activity was possibly not fully recovered (73% and 52% of control activities in males and females, respectively). This is a valid ancillary study of a design not applicable to SB-950 data requirements. Aldous, 11/12/96.

**269-232 135084 Brooks, W. and B. Broxup, "An acute study of the potential effects of orally administered aldicarb sulfone on behavior, neurochemistry, and neuromorphology in rats", Bio-Research Laboratories Ltd., Project ID #97351, 2/10/95. Twelve CrI:CD@(SD)BR rats/group were dosed once with aldicarb sulfone (99.9%) by gavage at 0, 1, 10, or 20 mg/kg. FOB and motor activity testing was done at prestudy, day 0 (beginning within 1 hr after dosing), day 7 and day 14. On day 15, 6/sex were perfused for neuropathology examinations. All treatment-related findings were limited to the "day 0" evaluations. There was no definitive NOEL: pinpoint pupils were elicited in both sexes at 1 mg/kg (statistically significant in males). Common FOB effects at 10 and 20 mg/kg were tremors, gait incapacity, reduced locomotor activity, reduced arousal

level, reduced reflexes to touch, pain, or visual stimuli, muscle weakness and reduced muscle tone, reduced urination and defecation, increased salivation, and reduced body temperature. Motor activity counts were remarkably reduced. There was no neuropathology effect. Originally not accepted, due to lack of positive control data. **Accepted** on receipt of requested data in Record Nos. 160090 to 160095, above. No "adverse effects" are indicated. Aldous, 11/21/96 and 11/20/98.

269-231 135083 Brooks, W. and B. Broxup, "An acute study of the potential effects of orally administered aldicarb sulfoxide on behavior and neuromorphology in rats", Bio-Research Laboratories Ltd., Project ID #97350, 2/2/95. Twelve CrI:CD@ (SD)BR rats/group were dosed once with aldicarb sulfoxide (98.9%) by gavage at 0, 0.05, 0.1, or 0.5 mg/kg. FOB and motor activity testing was done at prestudy, day 0 (beginning ½ hr after dosing), day 7 and day 14. On day 15, 6/sex were perfused for neuropathology examinations. Treatment-related findings were limited to the "day 0" evaluations. There was no NOEL. Incidence of pinpoint pupils was elevated in all dose levels in females and at 0.1 and 0.5 mg/kg in males. A non-significant increase in incidence was also seen in 0.05 mg/kg males. A statistically significantly reduced "rearing" score in 0.1 mg/kg males and slight tremors in one 0.1 mg/kg female were plausible treatment effects. Other findings were limited to 0.5 mg/kg. Common FOB effects at 0.5 mg/kg included tremors, gait incapacity (minor), reduced locomotor activity, reduced arousal level, reduced reflexes to pain or visual stimuli, muscle weakness and reduced muscle tone, reduced defecation, increased salivation and lacrimation, and reduced body temperature. Motor activity counts were remarkably reduced in 0.5 mg/kg males and females. There was no neuropathology effect. Originally not accepted, due to lack of positive control data. **Accepted on receipt of requested data in Record Nos. 160090 to 160095, above. No "adverse effects" are indicated. Aldous, 12/12/96 and 11/20/98.

269-237 142239 Robinson, K., W. Brooks, and B. Broxup, "A 13-week study of the potential effects of orally administered aldicarb technical on behavior, neurochemistry and neuromorphology in rats", Bio-Research Laboratories Ltd., Project No. 97234, Oct. 4, 1995. CrI:CD@ (SD)BR rats, 27/sex/group were dosed by gavage with 0, 0.05, 0.2, or 0.4 mg/kg/day aldicarb technical, 98.9%. Twelve/sex/group were designated for FOB/motor activity studies. Six/sex/group of these 12 were utilized for neuropathology at 13-wk termination. The remaining 15/sex/group were used for cholinesterase inhibition studies, with 5/sex/group sacrificed at weeks 4, 8, or 13. Cholinesterase assays were done on blood sampled before dosing began, as well as just before daily dosing and about 45 min after daily dosing at weeks 4, 8, and 13. Brains were collected for cholinesterase activity studies when these 3 groups were terminated at about 45 min after the respective final daily dosings. No NOEL was found for the FOB (pinpoint pupils and lack of pupillary reflex were dose-related at all treatment levels in both sexes). There was no cholinesterase NOEL, since RBC and plasma cholinesterase activities were inhibited at all dose levels. Tremors were the major FOB effects at 0.2 and 0.4 mg/kg/day. Motor activity was significantly decreased and cholinesterase activity was significantly reduced in most brain regions at those dose levels. Originally not accepted, due to lack of positive control data. **Accepted on receipt of requested data in Record Nos. 160090 to 160095, above. **No "adverse effects" are indicated**, since findings are reversible and consistent with well-known cholinesterase inhibition. Aldous, 12/2/96 and 11/20/98.

269-238 142240 Weiler, M.S., "Developmental neurotoxicity study with aldicarb in rats", Hazleton Wisconsin, Inc., 10/10/95. Project ID: HWI 6224-213. The study evaluated effects of aldicarb dosing of F0 females on developmental neurotoxicity in offspring. Thirty mated F0 CrI:CD@ (SD)BR VAF/Plus® females/group were dosed daily by gavage with 0, 0.05, 0.1, or 0.3 mg/kg/day aldicarb (98.9%) from gestation day (GD) 6 until lactation day (LacD) 10. [An initial

high dose level of 0.4 mg/kg/day was quickly reduced to 0.3 mg/kg/day, due to excessive toxicity]. Primary study evaluations were FOB evaluations on dams (pretest, GD 6, and LacD 7) and pups (postnatal days 14, 21, 35, and 63); motor activity counts on pups (postnatal days 13, 17, 21, and 60); cholinesterase evaluations of dams (pretest, GD 7, LacD 7, and LacD 11) and pups (LacD's 4, 10, and 11); and neuropathological examinations of pups on postnatal days 11 and 60. Maternal FOB tests and blood sampling for cholinesterase activity were typically done 2 hr after respective daily treatments (i.e., after peak response time). Apparent maternal cholinesterase inhibition NOEL = 0.1 mg/kg/day (RBC and plasma cholinesterase inhibition at 0.3 mg/kg/day). Apparent maternal toxicity NOEL = 0.05 mg/kg/day (pupillary miosis in 1 dam at 0.1 mg/kg/day and in all high dose dams). Maternal clinical signs consistent with acute cholinesterase enzyme inhibition common at 0.3 mg/kg/day included tremors, ataxia, excessive lacrimation and salivation, and stained fur. Developmental toxicity NOEL = 0.05 mg/kg/day (increased stillborn pups, body weight decrement in post-weanling males, and reduced hindlimb grip strength and foot splay in F1 females on postpartum day 35). The latter findings appeared to be mediated by maternal toxicity (stillborn pup incidence), were small in magnitude, and/or were not convincingly treatment related (see discussion section of review). Not acceptable, but upgradeable (no positive control data for FOB or histopathology). Aldous, Jan. 8, 1997.

NEUROTOXICITY VALIDATION OR POSITIVE CONTROL STUDIES

NOTE: Full one-liners for record Nos. 156317 to 156321 are found in the Cyclanilide review, w145936.sup, and/or in the Summary of Toxicology Data for Cyclanilide under DPN # 52093.

269-248 160090 [Copy of an acceptable validation study submitted in support of Cyclanilide]: 52093-080 156318 Beyrouy, P., "An acute neurotoxicity study of the effects of orally administered DDT and trimethyltin chloride in rats", Bio-Research Laboratories Ltd., Nov. 4, 1994. Project ID #29537.

269-249 160091 [Copy of an acceptable validation study submitted in support of Cyclanilide]: 52093-079 156317 Beyrouy, P., "An inter-observer reliability (IOR) study for grip strength and hindlimb splay measurements in rats", Bio-Research Laboratories Ltd., Nov. 4, 1994. Project ID #29539.

269-250 160092 [Copy of an acceptable validation study submitted in support of Cyclanilide]: 52093-081 156319 Beyrouy, P., "A subchronic neurotoxicity study of the effects of orally administered acrylamide in rats", Bio-Research Laboratories Ltd., Nov. 4, 1994. Project ID #29538.

269-251 160093 [Copy of an acceptable validation study submitted in support of Cyclanilide]: 52093-082 156320 Beyrouy, P., "An inter-observer reliability (IOR) study for qualitative functional observational battery assessments in rats", Bio-Research Laboratories Ltd., Nov. 4, 1994. Project ID #29540.

269-252 160094 [Copy of an acceptable validation study submitted in support of Cyclanilide]: 52093-083 156321 Beyrouy, P., "An acute neurotoxicity study of the effects of orally administered carbaryl and triadimefon in rats", Bio-Research Laboratories Ltd., Nov. 4, 1994. Project ID #29546.

269-253 160095 Beyrouy, P., "An acute study of the potential effects of orally administered triadimefon on behavior in rats", Bio-Research Laboratories Ltd., 11/19/92. Project No. 97132. This study was completed about 2 years before Record No. 160094, above, and is less detailed

compared to the later study. Findings were comparable to the later study [increased motor activity, increased rearing activity, and alterations in walking posture (walking with raised pelvis)]. Only summary data are included in this report. These data are less useful in methods validation than are the later studies. Aldous, 11/20/98.

METABOLISM STUDIES

269-246 148580 Andrawes, N. R., H. W. Dorough, and D. A. Lindquist, "Degradation and elimination of Temik in rats", Journal of Economic Entomology 60: 979-987 (1967). Aldicarb was rapidly metabolized after oral dosing in rats, and was excreted primarily in the urine. Aldicarb sulfoxide and other sulfoxide derivatives were the primary identified metabolites. Only traces of parent aldicarb were found. No DPR review is indicated. Aldous, 1/3/97.

A SERIES OF FIFRA-TYPE STUDIES ON ALDICARB SULFONE (typically older studies)

ONCOGENICITY, MOUSE (on aldicarb sulfone)

099, 121 050796, 056628 "Aldicarb Sulfone 18-Month Feeding in the Diet of Mice", (Carnegie-Mellon Institute of Research, 3-25-77, Project report 40-38), Aldicarb sulfone, 99.76%, was fed to COBS CD-1 mice in the diet at 0, 0.15, 0.6, 2.4, or 9.6 mg/kg/day for 18 months, 50/sex/group, 2 control groups for a total of 100/sex/control. No effect seen on tumor incidences or other criteria examined. Nominal oncogenicity NOEL \geq 9.6 mg/kg/day. Deficiencies: There are no daily observations, no organ weights, no individual body weights, no analyses of diet. Supplemental data. (D. Shimer and J. Gee, 11/23/87)

100 050797, Exact duplicate of 050796, volume 099.

REPRODUCTION, RAT (on aldicarb sulfone)

120 056625, "Aldicarb Sulfone Inclusion in the Diet of Rats for Three Generations, Dominant Lethal Mutagenesis and Teratology Studies", (Carnegie-Mellon Institute of Research, 1/11/77), Aldicarb sulfone, 99.76%, was given to Harlan-Wistar rats in the diet at 0, 0.6, 2.4 or 9.6 mg/kg/day for a 3 generation, 1 litter/generation study. Mated 10 males and 20 females at 100 days of age in each group. No adverse effects reported. Deficiencies: inadequate individual data including body weight, litter data, inadequate necropsy and histopathology on parental animals with appendices of data not included, protocol too brief. Supplemental data. (D. Shimer and J. Gee, 11/23/87)

098 051231, "Aldicarb sulfone: Inclusion in the Diet of Rats for Three Generations, Dominant Lethal and Teratology Studies", (Carnegie-Mellon, 1/11/77, Report 40-1). Missing even-numbered pages.

TERATOLOGY, RAT (on aldicarb sulfone)

098 050792, "Aldicarb sulfone: Inclusion in the Diet of Rats for Three Generations, Dominant Lethal and Teratology Studies", (Carnegie-Mellon, 1/11/77, Report 40-1.) Missing even-numbered pages. See 056625 below.

120 056625, "Aldicarb Sulfone Inclusion in the Diet of Rats for Three Generations, Dominant Lethal Mutagenesis and Teratology Studies", (Carnegie-Mellon Institute of Research, Report 40-1, 1/11/77) Aldicarb sulfone, 99.76%, was fed to Harlan-Wistar rats in the diet at 0, 0.6, 2.4 or 9.6 mg/kg/day in three different dosing regimes; a. from day of vaginal plug to day 20, b. days 6-15 of gestation, c. days 7,8,9 of gestation. There were 17 or 18 rats in each group. No adverse effects reported. Deficiencies: No dose justification, no analysis of diets, no food consumption for a dietary study; unusual protocol and not fully described, fetuses not sexed. Supplemental data. (D. Shimer 11/9/87 and J. Gee, 11/16/87)

GENE MUTATION (on aldicarb sulfone)

098 050790, "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay", Aldoxycarb, (Pharmakon, 3/85, PH 314-UC-002-84), Aldicarb sulfone, Lot # HTS 4842AC, no purity stated; CHO/HGPRT assay with and without rat liver activation at 0, 500, 750, 1000, 1250 or 1500 ug/ml, 5 hours; unacceptable (single trial, no purity stated). Supplemental data. (J. Gee, 1/29/87)

CHROMOSOMAL ABERRATIONS (on aldicarb sulfone)

131 065863, "CHO Metaphase Analysis. In Vitro Chromosome Aberration Analysis in Chinese Hamster Ovary Cells (CHO)", (Pharmakon Research International, Inc., PH 320-UC-005-83, 5/25/84), Technical grade Aldoxycarb = Aldicarb sulfone (no lot #; no purity) was applied to duplicate cultures of Chinese Hamster Ovary cells (CHO-K1-BH4) at 0, 50, 250, and 500 ug/ml with and without activation; a repeat assay used 400, 500, and 600 ug/ml without activation; harvest was 14-18 hours post-treatment; 100 cells/dose level were scored. No adverse effect-an increased frequency of aberrations (no activation) in the high dose group was not confirmed in

the repeat assay. Supplemental study-the test material was aldicarb sulfone, not aldicarb. (B. Davis 9/9/88)

098 050791, "Aldicarb sulfone: Inclusion in the Diet of Rats for Three Generations", (Carnegie-Mellon, 1/11/77, Report 40-1) Incomplete with even-numbered pages missing. (J. Gee, 1/29/87)

120 056625, "Aldicarb Sulfone Inclusion in the Diet of Rats for Three Generations, Dominant Lethal Mutagenesis and Teratology Studies", (Carnegie-Mellon Institute of Research, Report 40-1, 1-11-77), Aldicarb sulfone, 99.76% was given to male Harlan-Wistar rats in the diet at 0, 0.6, 2.4 or 9.6 mg/kg/day. F2 males from a reproduction study, after being dosed for 155 days, were bred to untreated females, 15 females were mated at each dose level, weekly for 10 weeks. No adverse effect reported. Deficiencies: protocol too brief, unusual schedule. Supplemental data. (D. Shimer and J. Gee, 11/23/87)

NEUROTOXICITY (on aldicarb sulfone)

098 050794, "Neurotoxicity Evaluation of UC 21865 in White Leghorn Hens (*Gallus domesticus*)", (Food and Drug Research Labs, 1/26/77, No. 5233), Aldicarb sulfone (4 lots, no purity stated); by oral gavage at 250 mg/kg b. wt., days 1 and 21; no adverse neurotoxic effects; 40 hens in test group, 10 controls; unacceptable (no purity stated, no histopathology because there were no neurotoxic signs.) Supplemental data. (J. Gee, 1/29/87)

MISCELLANEOUS REPORTS AND REVIEWS (NOT SB-950 STUDIES)

269-208 115442 and 121395 (segments of a single report). Wyld, P. J., C. E. Watson, W. S. Nimmo, and N. Watson, "A safety and tolerability study of aldicarb at various dose levels in healthy male and female volunteers", ICR Project No. 003237, March 11, 1992. This study was reviewed by the DPR Product Data Review Group (T. Moore) on 7/7/92. The worksheet is included in the volume.

269-207 116141 "Epidemiology of aldicarb exposure in humans: A critique of the literature with emphasis on its application to risk assessment" (volume has been assigned to Worker Health and Safety Branch for review). Aldous 1/3/97.

138 066946, "Aldicarb: Special Review Technical Support Document", US EPA, June 1988. Document contains information on both Aldicarb and Aldicarb Sulfone. Reference volume; no worksheet. (H. Margolis and J. Gee, 10/11/88)

077 042542, Summary of 7 day studies with aldicarb/aldicarb sulfoxide.

089 047800, Review of paper on immune competence and aldicarb exposure.

089 047801, Summary information for immune function effects associated with aldicarb exposure.

089 047802, "Chronic Exposure to Aldicarb Contaminated Groundwater and Human Immune Function", (Wisconsin Division of Health).

089 047803, 047804, Review of 047802.

089 055546, Supplemental to 047802.

108 050806, "Relationship between Short and Long-Term Feeding Studies in Designing an Effective Toxicity Test", (Agricultural and Food Chemistry Vol. 11, no. 6, Nov.-Dec. 1963, pp. 436-491).

108 051471, "Selection of the Valid Number of Sampling Units and a Consideration of their Combination in Toxicological Studies Involving Reproduction, Teratogenesis or Carcinogenesis", (Fd. Cosmet. Toxicol. Vol. 8, pp. 177-182. Pergamon Press 1970).

033 922545, Stability information for aldicarb and metabolites.

097 051470, "Pesticide Residues in Food: 1979 Evaluation. ...1982 Evaluation". (WHO Expert Group, Food and Agriculture organization of the UN). The 1979 evaluation reviewed a number of studies on aldicarb and the 1982 evaluation, aldicarb sulfone. The conclusion on aldicarb was that the studies reviewed were negative for adverse effects and that mutagenicity studies and a cholinesterase study in dogs were still needed. The latter has subsequently been addressed. (Gee, 1987, and Aldous, 1991).

155 073742 "Immunotoxicology Study of Aldicarb in Mice: Phase II." (ITT Research Institute, Chicago, IL, 1/89). Aldicarb, no purity stated, given in the drinking water to groups of 12 female B6C3F1 mice at 0, 1, 10 or 100 ppb for 34 days, verified analytically; the immune profile included ability of natural killer (NK) cells to lyse YAC-1 lymphoma, sensitized cytotoxic T-lymphocytes to lyse P815 tumor cells; spleen cell viability, cellularity and percentages of total T-cells, T-suppressor, T-helper and B lymphocytes were investigated; cyclophosphamide as positive control. Spleen, thymus, kidney and liver organ weights were determined. There were no statistically significant effects on any parameter. Supplementary data. (Gee, 12/28/89)